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8508 '99 AUG 27 A10:03

August 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-0529
"Changes to an Approved NDA or ANDA" Draft Guidance
Comments to the Agency

Dear Sir or Madam:

The purpose of this communication is to comment on the Draft Guidance dated 6/16/99, "Changes to an Approved NDA or ANDA". We wish to offer the following:

Comment 1: (Lines 86 and 87, page 4)

We believe that the terminology *"...condition...beyond the variations..."* is vague and needs clarification. If examples could be provided, perhaps the terminology would be more easily understood.

Comment 2: (Line 89, page 4)

We believe that additional regulatory burden is created by the wording *"...list all changes..."*. The provisions of the Annual Report do not allow significant changes, so the listing of all the minor changes in the cover letter of the report would accomplish little. The changes are properly delineated in the various sections of the report as required.

It is common practice to summarize the changes in the cover letter of a supplemental application. The requirement for a detailed listing of all changes in the cover letter of a supplement complicates and perhaps confuses the submission's purpose and understanding.

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Comment 3: (Lines 105 to 114, pages 4 and 5)

The word *"validate"* should be changed to *"assess"*. In addition, the requirement to submit *"....include the information developed by the applicant in validating (assessing) the effects of the change..."* increases the regulatory burden of the filing. All information is not necessary, may be too voluminous and not contributory to the understanding of the reviewer. A comprehensive summary with rationale, outcome, and discussion of how it supports the change is more appropriate. All of the data can be available for inspection by the Field, if necessary.

Comment 4: (Lines 154 to 166)

In order to further define "equivalence" within the context of this section, it may be of assistance to refer to other existing guidances for examples of equivalence testing.

Comment 5: (Lines 259 to 261, page 9)

Line 259 should be revised to read *"(2) changes that could significantly affect contamination..."*. In addition, the intent of (3) should be clarified as to its application to drug substance and/or drug product. Examples of methods of sterilization and microbiological controls would clarify the scope of the statement.

Comment 6: (Line 272, page 9)

The term "refurbished" should be deleted or further defined by examples.

Comment 7: (Line 392, page 13)

The words *"that extend the filling time into additional aseptic filling shifts or"* should be deleted from the sentence. The change of shift and shift personnel should be covered in the media fill process simulation, therefore this statement is not necessary.

Comment 8: (Line 400 and 401, page 13)

For clarification, the phrase should be revised to read *"....filter materials or filter pore size..."*. Add "pore" for clarity.

Comment 9: (Line 439, page 14)

For clarification, the phrase should be revised to read "...filter materials or pore size)". Add "pore" for clarity.

Comment 10: (Line 443, page 15)

For clarification, the phrase should be revised to read *"....dual product sterilizing filters in series..."*. Add "in series".

Comment 11: (Lines 457 to 461, page 15)

The bullet point should be revised to read *"Changes to aseptic processing methods that do not increase bulk solution storage time by more than 50 percent beyond the validated limits in the approved application"*. Without revision, the regulatory burden is increased as all scale changes are supplements, rather than Annual Report.

Comment 12: (Lines 567 to 571, page 18)

The language of point #1 increases regulatory burden because previously any compendial revision was annual reportable. All compendial changes consistent with FDA requirements should be subject to annual report without qualification.

Comment 13: (Lines 596 to 602, pages 19 & 20)

The section mentions plastics, rubbers, inks and adhesives that have previously been approved by CDER. Yet, the information relative to what CDER has and has not approved is not generally accessible to the industry. We hope CDER can make available on its website the information relative to this section.

Comment 14: (Lines 604 and 605, page 20)

For clarification, the phrase should be revised to read *"...(4) changes may significantly affect sterility assurance...."*.

Comment 15: (Lines 657 to 660, page 21)

Point #1 should also be applicable to sterile drug products, not just nonsterile drug products.

Comment 16: (Line 776 to 777, page 25)

Point #2 should be revised to read *"Changes that significantly affect product sterility assurance...."*.

We appreciate being able to have the opportunity to comment on the draft guidance. If you need any additional information or have any questions concerning this request, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

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